Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study☆

Mie Jareid [a,*], Jean-Christophe Thalabard [b], Morten Aarflot [a], Hege M. Bøvelstad [a], Eiliv Lund [a], Tonje Braaten [a]

[a] Department of Community Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway
[b] Applied Mathematics Lab, UMR CNRS 8145, Paris Descartes University, USPC, Paris, France

HIGHLIGHTS

- We present a population-based prospective cohort study of LNG-IUS users.
- A mean of 4 years use was associated with 47% reduced ovarian cancer risk.
- Endometrial cancer risk was reduced by 78%.
- We found no association between LNG-IUS use and breast cancer.

ARTICLE INFO

Article history:
Received 15 November 2017
Received in revised form 28 January 2018
Accepted 10 February 2018
Available online xxxx

Keywords:
Epidemiology
Prospective cohort study
Ovarian neoplasms
Uterine neoplasms
Breast neoplasms
Intrauterine device
Intrauterine device, medicated
Levonorgestrel
Levonorgestrel-releasing intrauterine system
Hormonal contraceptives

ABSTRACT

Objective. Women with ovarian cancer have poor survival rates, which have proven difficult to improve; therefore primary prevention is important. The levonorgestrel-releasing intrauterine system (LNG-IUS) prevents endometrial cancer, and recent studies suggested that it may also prevent ovarian cancer, but with a concurrent increased risk of breast cancer. We compared adjusted risks of ovarian, endometrial, and breast cancer in ever users and never users of LNG-IUS.

Methods. Our study cohort consisted of 104,318 women from the Norwegian Women and Cancer Study, 9144 of whom were ever users and 95,174 of whom were never users of LNG-IUS. Exposure information was taken from self-administered questionnaires, and cancer cases were identified through linkage to the Cancer Registry of Norway. Relative risks (RRs) with 95% confidence intervals (CIs) were estimated with Poisson regression using robust error estimates.

Results. Median age at inclusion was 52 years and mean follow-up time was 12.5 (standard deviation 3.7) years, for a total of 1,305,435 person-years. Among ever users of LNG-IUS there were 18 cases of epithelial ovarian cancer, 15 cases of endometrial cancer, and 297 cases of breast cancer. Whenever users were compared to never users of LNG-IUS, the multivariable RR of ovarian, endometrial, and breast cancer was 0.53 (95% CI: 0.32, 0.88), 0.22 (0.13, 0.40), and 1.03 (0.91, 1.17), respectively.

Conclusion. In this population-based prospective cohort study, ever users of LNG-IUS had a strongly reduced risk of ovarian and endometrial cancer compared to never users, with no increased risk of breast cancer.

Abbreviations: BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; LNG-IUS, levonorgestrel-releasing intrauterine system; NOWAC, Norwegian Women and Cancer; OC, oral contraceptives; PY, person-years; RR, relative risk; SD, standard deviation; SIR, standardized incidence ratio.

☆ Disclaimer: Some of the data in this article are from the Cancer Registry of Norway. The Cancer Registry of Norway is not responsible for the analysis or interpretation of the data presented.

* Corresponding author at: Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Pb 6070 Langnes, NO-9037 Tromsø, Norway.
E-mail addresses: mie.jareid@uit.no (M. Jareid), Jean-Christophe.Thalabard@parisdescartes.fr (J.-C. Thalabard), morten.aarflot@uit.no (M. Aarflot), hege.m.bovelstad@uit.no (H.M. Bøvelstad), eiliv.lund@uit.no (E. Lund), tonje.braaten@uit.no (T. Braaten).

https://doi.org/10.1016/j.ygyno.2018.02.006
0090-8258/

1. Introduction

In 2012, ovarian cancer caused an estimated 152,000 deaths worldwide [2]. The cumulative risk of ovarian cancer until age 75 is 1.3% in Norway and is similar in the United States [3,4]. The symptoms of ovarian cancer are vague, and there is no screening test. This has led to problems of late diagnosis and a 5-year survival of <50% [5]. Thus, ovarian cancer ranks eighth in cancer incidence, but fifth in cancer mortality among women [4]. Primary prevention therefore remains the best available measure against ovarian cancer [5].

Risk of ovarian cancer is reduced by 15–29% for every 5 years of oral contraceptive (OC) use, and globally, OC use prevents an estimated 30,000 cases of ovarian cancer each year [6]. Long-term OC use also reduces the risk of endometrial cancer, with 5–9 years of use reducing the risk by 34% [7]. However, OC use increases the risk of breast cancer by up to 38% with >10 years use, and for a minimum of 5 years after cessation [8,9], in addition to carrying other health risks. Prescribing OCs for ovarian cancer prevention to women who do not need contraception is not recommended [10].

The levonorgestrel-releasing intrauterine system (LNG-IUS) was introduced in Norway in 1994. In the Nordic countries, LNG-IUS is the second-most used form of contraception after OCs, and it is the most commonly used form of long-acting reversible contraception [11]. Recently, three Finnish studies have shown that, compared to the general population, LNG-IUS users have a standardized incidence ratio (SIR) of 0.59 for ovarian cancer and 0.46 for endometrial cancer [12,13], but also an increased risk of ductal and lobular breast cancer (SIR 1.20 and 1.33 respectively, increasing to SIR 1.37 and 1.73 with >5 years of use) [14]. However, these studies did not adjust for other hormonal risk factors.

Our study aim was to combine self-reported information on OC use and reproductive factors from the Norwegian Women and Cancer (NOWAC) Study, with registry-based follow-up of cancer cases to compare adjusted risks of ovarian, endometrial, and breast cancer in ever users and never users of LNG-IUS. We also included estimates of the reduction in the risk of endometrial cancer in this nationally representative cohort, given the well-known preventive effect of LNG-IUS use on this cancer [15].

2. Methods

2.1. Study cohort

The NOWAC Study is a population-based prospective cohort study designed to investigate the association between hormone use and hormone-dependent female cancers [16]. During 1991–2007, women born between 1927 and 1965 were randomly selected from the Norwegian Population Registry and were sent a questionnaire along with a letter that explained the study. Those who returned a completed questionnaire were enrolled. Statistics Norway replaced participants' names and personal identification numbers with serial numbers for use by researchers. Recruitment took place in two waves: 102,540 participants were enrolled in 1991–1997 (response rate 57%), and 63,232 participants in 2003–2006 (response rate 48.4%). The external validity of the NOWAC Study was found to be good [17]. Follow-up information has been collected up to two times after enrollment.

The NOWAC questionnaires targeted LNG-IUS use as from 1998 by the question: Have you ever used a hormone intrauterine device? A total of 145,320 women completed a questionnaire during 1998–2006, either at enrollment or as part of follow-up. From these, we excluded 33,182 that either did not answer the question on hormone intrauterine device or had a hysterectomy or oophorectomy; 4813 that either had prevalent cancer or died or emigrated before the start of follow-up; 2938 that indicated LNG-IUS use before the device was available in Norway, and seven for technical reasons. Thus the final study cohort consisted of 104,380 women, of which 9146 were ever users of LNG-IUS.

2.2. Exposure assessment

In addition to questions on LNG-IUS (ever use, duration of use, age at first use, current use), we identified eight exposure variables associated with ovarian, endometrial, or breast cancer [18], regardless of their association with LNG-IUS use: age at start of follow-up (41–76 years, in 4-year increments), body mass index at enrollment (BMI, <25 kg/m2, ≥25 kg/m2), physical activity level at enrollment (very low, low, intermediate, high, very high), maternal history of breast cancer (yes, no), age at menarche (<12, 12–14, ≥15), ever use of OCs (yes, no), parity (0, 1–2, 3–4, ≥5), and menopausal status at start of follow-up (pre, *peri*, post, unknown). Unknown menopausal status was given to those who used hormone replacement therapy, those who indicated that menses had stopped due to "medication, illness, exercise, or other" and to those who did not answer the question.

2.3. Outcomes

Primary cancers were identified through linkage to the Cancer Registry of Norway using the International Classification of Diseases, Revision 7 (ICD-7) codes. All citizens were identified by their personal identification number upon contact with health care providers, who are obliged to report all cancer cases to the Cancer Registry of Norway. Outcomes were defined as primary cancer of the ovary including the fallopian tube (ICD-7 code 175), cancer of the uterine corpus (ICD-7 code 172), and cancer of the breast (ICD-7 code 170). In order to restrict the analyses to epithelial ovarian cancer and endometrial cancer, non-carcinoma cancers of the ovary and uterine corpus were excluded from the analyses ($n = 62$). Deaths and emigrations were identified through the Cause of Death Registry and Statistics Norway. Follow-up ended on 31 December 2015.

2.4. Statistical analysis

We calculated person-years (PY) of follow-up from the date of entrance into, until the date of exit from the study. Exit date was defined as the date of cancer diagnosis, emigration from Norway, death, or end of follow-up, whichever occurred first. We used chi-squared tests of independence to compare the characteristics of ever users and never users of LNG-IUS, and to compare selected characteristics of those who did and did not answer the question on LNG-IUS use.

We calculated crude cancer incidence rates with 95% confidence intervals (CIs) assuming a Poisson distribution. Relative risks (RRs) and their 95% CIs were estimated with Poisson regression using a robust error estimate [1]. Adjusted RR models were built in a stepwise backward manner by removing nonsignificant covariates from the full model, with listwise deletion of participants with missing information. Model fit was assessed by testing the deviance versus its assumed chi-squared distribution. Statistical significance was defined as a test resulting in a p-value <0.05. We performed an additional analysis of the association between LNG-IUS use and endometrial cancer, stratified by ever OC use (yes, no), and did a Wald test of heterogeneity between the resulting RRs. We performed two additional analyses of the association between LNG-IUS use and breast cancer: one stratified by duration of use (≤5 and >5 years), and the other stratified by current and former users at the start of follow-up.

The analyses were performed in SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

2.5. Ethics

The Regional Ethics Committee, REK Nord, approved the NOWAC Study. Written information was provided to the participants, and return

Please cite this article as: M. Jareid, et al., Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without in..., Gynecol Oncol (2017), https://doi.org/10.1016/j.ygyno.2018.02.006